Autonomic Neuroscience: Basic and Clinical 180 (2014) 1–4

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Highlights in basic autonomic neurosciences: Is an increase in sympathetic nerve activity involved in the development and maintenance of hypertension?

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ARTICLE INFO

Keywords:
Arterial pressure
Hypertension
Sympathetic nerve activity
Telemetry

ABSTRACT

The 21st century has brought renewed energy to the field of neural control of the cardiovascular system with interest in assessing directly the role of sympathetic nerve activity (SNA) in initiating and/or maintaining an elevated level of arterial pressure in animal models of cardiovascular disease and in human subjects. Below is a review of some recent studies that use continuous nerve recordings of SNA to look at the time course of changes in activity as hypertension develops. These studies have advanced our understanding of the role of SNA in hypertension, but they also leave us wanting to know more.

Introduction

The recent use of a catheter-based radiofrequency renal denervation technique has been successful in reversing the heightened levels of arterial pressure (AP) and muscle sympathetic nerve activity (MSNA) in a cohort of hypertensive patients with end stage renal disease (Schlaich et al, 2009). Although it remains to be determined whether the reversal of these markers of the pathology reflects disruption of renal afferent or efferent fibers, these findings have drawn attention to the role of altered SNA (renal SNA in particular) in cardiovascular disorders. They also highlighted the need to perfect methodologies for chronic sympathetic nerve recordings in animal models of cardiovascular disease that would finally allow for an assessment of the time course of changes in SNA as a disease develops and progresses. Questions that had plagued the field for many years are now approachable. We can move from "assuming" SNA is increased (or decreased) to actually proving or disproving such. Even studies using human subjects cannot judge precisely the time course of changes in SNA that might occur as hypertension develops unless the investigators had the good fortune to study the same individual before and during development of hypertension.

Yoshimoto, M., Miki K., Fink G.D., King A., Osborn J.W., 2010. Chronic angiotensin II infusion causes differential responses in regional sympathetic nerve activity in rats. Hypertension 55, 644–651.

Article summary

This study used direct recordings of renal and lumbar SNA (RSNA, LSNA) in conscious male rats to test the hypothesis that an increase in SNA contributes to the hypertension induced by the chronic infusion of angiotensin II (Ang II; 150 ng/kg/min, sc) in rats on a high-salt (2% NaCl) diet (HSD). AP, RSNA, and LSNA were continuously recorded for 21 days, including a 5-day control period, an 11-day treatment period (Ang II or vehicle), and a 5-day recovery period. AP was monitored via telemetry; SNA was recorded via implanted stainless electrodes with wires tunneled to the scapular region ("tethered" technique). AP and SNA remained steady for the 21-day recording period in vehicle-treated rats on an HSD. The time course of Ang II-induced changes in mean AP confirmed earlier findings; specifically, AP began to increase on day 1, reached a maximum of ~35 mmHg above control level within a few days, and recovered when Ang II infusion was stopped. In contrast to expectations, neither RSNA nor LSNA was elevated. RSNA ($n = 8$) was reduced by ~40% during the first 7 days of Ang II infusion and then began to recover partially by day 10. LSNA ($n = 7$) was unchanged throughout the 21-day recording period.

Commentary

This study warrants special attention as it was the first to use continuous recordings of both RSNA and LSNA during the development of hypertension. By recording from two functionally distinct sympathetic outflows, they were able to entertain the question of whether Ang II and salt work synergistically to affect SNA uniformly. Earlier work using indirect measures of SNA (a depressor response to ganglionic block and whole body NE spillover) had implied a global sympathoexcitation. Since RSNA was reduced and LSNA was unchanged with Ang II treatment

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http://dx.doi.org/10.1016/j.autneu.2013.07.004

in rats on an HSD, a global increase in SNA is obviously not the basis for hypertension in this model. The data also point to a non-uniform action of Ang II on sympathetic outflow.

The authors cite other work which suggested that the reduction in RSNA was baroreceptor mediated. It is unfortunate that they did not assess baroreceptor reflex function in this study. Since sustained increases in AP can lead to resetting of the baroreceptor reflex, it is somewhat surprising that RSNA would remain nearly completely suppressed for so many days. And curiously, why was LSNA not subjected to the same baroreceptor-mediated inhibition? They propose that an Ang II-mediated increase in LSNA is buffered by the baroreceptors such that no change occurs; yet one might expect at least a subtle hint that Ang II could increase LSNA, even transiently. Are we to assume that the Ang II-mediated increase in LSNA was perfectly matched by the baroreceptor-mediated inhibition of LSNA?

The big question remains: What sympathetic outflow is activated to account for the neurogenic component of the elevation in AP with Ang II infusion in rats on an HSD? In which vascular bed is resistance increased to contribute to the hypertension? There is much work yet to be done.

Guild S.-J., McBryde F.D., Malpas S.C., Barrett C.J., 2012. High dietary salt and angiotensin II chronically increase renal sympathetic nerve activity: a direct telemetric study. Hypertension 59, 614–620.

Article Summary

This study was designed to test the hypothesis that RSNA is chronically elevated when AP is gradually increased during a slow rate of infusion of Ang II in rabbits on an HSD. AP, heart rate (HR), and RSNA were continuously recorded for 26 days (5 days of baseline; 21 days of treatment) by using telemetry in two groups of 6 rabbits each (male and female); a "Salt-Ang" group drank a 0.9% NaCl solution and received Ang II (20 ng/kg per min), and a "control" group drank tap water and was not infused with Ang II. AP, HR, and RSNA were unchanged throughout the recording period in the control group. In the Salt-Ang group, mean AP slowly increased to ~18 mm Hg above baseline levels over the first week and remained elevated for the next 2 weeks of treatment. During the time when AP was increasing, RSNA was unchanged. By about day 16 of treatment, RSNA tended to increase and was significantly elevated above baseline level on day 21. HR remained unchanged for the full experimental period. Baroreceptor reflex responses of HR and RSNA to infusions of phenylephrine and sodium nitroprusside were recorded on days 0 (baseline), 7, and 21. There was a shift to the right in the baroreceptor reflex function curve relating HR to AP on both days 7 and 21, suggesting baroreceptor resetting to a higher pressure. In terms of RSNA, there was a significant rightward shift on day 21, but not by day 7 when AP had increased; also RSNA could not be completely suppressed on day 21 with the phenylephrine-induced pressor response. They concluded that elevated Ang II levels chronically increases RSNA in rabbits on an HSD, and this may contribute to the maintenance (but not initiation) of hypertension.

Commentary

This study was specifically designed to avoid the baroreceptor reflex-mediated inhibition of RSNA that occurs with the "immediate" pressor response to administration of the higher dose of Ang II as in the study described above. This was done by using a lower dose of Ang II that gradually increased AP; however, the magnitude of the increase was less than that seen in the preceding study. The authors suggest that the rise in AP seen with this lower dose of Ang II (and presumably a lower plasma level) is due to a central action of the drug, whereas at least a component of the pressor response to a higher dose of Ang II is due to direct vasoconstriction.

The authors of this study should be applauded for the care they took to assure the stability of the nerve recording and for assessing the characteristic cardiac rhythmicity of SNA (Guild et al, 2010). The authors provide great detail about how they evaluated the recordings to assure that electrical noise was minimized, established a 0 voltage level, and a 100% level of sympathoexcitation during nasopharyngeal activation. This is very important when comparing activity over an extended period of time. This is not to say that others do not take the same care, but the details here provide an extra degree of confidence for the reader.

The assessment of the baroreceptor reflex responses in both HR and RSNA is another strength of this study. By showing the relationship between AP and both HR and RSNA, the authors could identify differences in how Ang II affected the cardiovagal versus sympathetic limbs of the reflex arc in rabbits on an HSD. Too often investigators make global conclusions that a perturbation affects the baroreceptor reflex based simply on the response in HR. Here, Ang II led to resetting of the vagal component of the reflex toward a higher AP by day 7 with no further change by day 21. The full range of HR (between ~125 and 325 beats/min) was preserved over an AP range of 40 to 160 mm Hg. The situation was very different for the sympathetic limb of the reflex. Resetting toward a higher AP was not seen until day 21, and the full range of amplitude modulation of RSNA was altered by Ang II. On day 21, RSNA was no longer able to be maximally inhibited even at a high AP level. The authors suggested that the lack of baroreceptor-mediated inhibition of RSNA might contribute to the ability of Ang II to sustain hypertension in animals on an HSD.

One concern about the conclusion that RSNA was increased on day 21 is that it achieved statistical significance only if RSNA was normalized to a maximum response with nasopharyngeal activation. When comparing absolute voltage values, the Ang II-mediated change in RSNA was not significant. Another concern is why the investigators terminated the experiment just at the point when RSNA became significantly elevated. Would extending the study for another few days have shown an even greater rise, and would the increase have reached significance even in terms of absolute voltage levels of RSNA? But perhaps they had reached the time limit for which they were confident the nerve recording was viable and stable.

This study contributed valuable information to the complex story of synergistic actions of Ang II and an HSD on the cardiovascular system. Yet no one has demonstrated directly that an increase in SNA to one or more vascular beds contributes to the early phase of hypertension in this model or even that a persistent increase in SNA contributes to the maintenance of hypertension. Chronic recordings of splanchnic SNA have yet to be used in this model of hypertension, but doing so might be enlightening since coeliac ganglionectomy markedly attenuated Ang II-mediated hypertension in rats on an HSD (King et al, 2007).

Armitage J.A., Burke S.L., Prior L.J., Barzel B., Eikelis N., Lim K., Head G.A., 2012. Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. Hypertension 60, 163–171.

Article summary

This study determined the rapidity of sympathetic activation in the presence of a high-fat diet (HFD) and determined if there is a link between diet-induced sympathetic activation and stress. AP and RSNA were recorded via telemetry in two groups of male rabbits; body weight, blood glucose, plasma insulin, and leptin levels were also monitored. One group ($n = 13$) was fed a high-fat diet (HFD) for 3 weeks followed by a control diet for 1 week, and a second group ($n = 10$) was fed a control diet for all 4 weeks. Baroreceptor reflexes and responses to air-jet stress were evaluated weekly. All parameters remained stable in rabbits on a control diet. Within 1 week of being on HFD, AP, HR, and RSNA were significantly increased above levels seen in control animals as were body weight, blood glucose, plasma